Synthesis and Preliminary Evaluation of Agents Incorporating the Pharmacophore of the Duocarmycin/Pyrindamycin Alkylation Subunit: Identification of the CC-1065/Duocarmycin Common Pharmacophore

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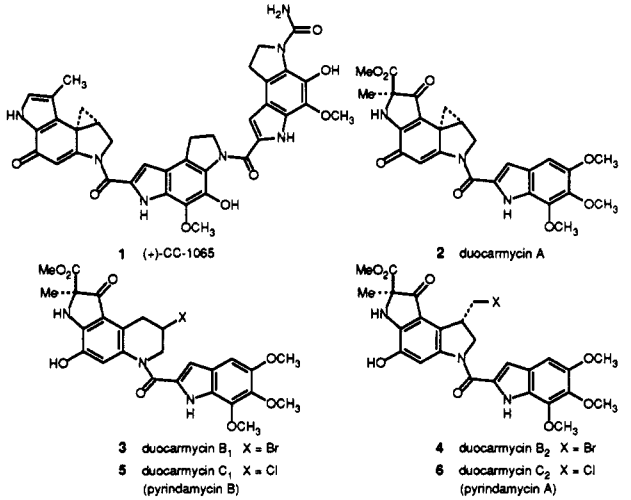
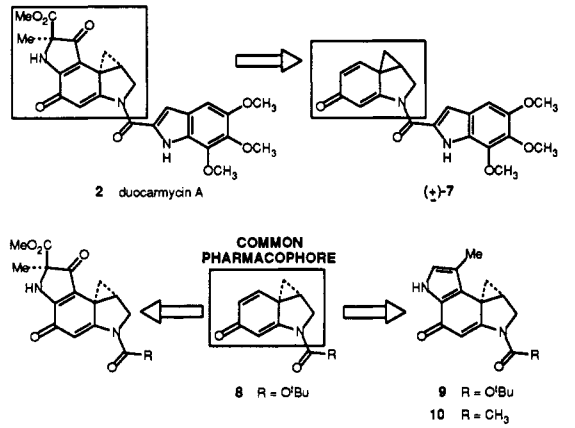
Summary: The synthesis of **7** (CI-TMI) incorporating the parent 1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one (CI) alkylation subunit of duocarmycin is described. The results of its comparative evaluation (in vitro cytotoxic activity, DNA covalent alkylation properties) illustrate that **7** (CI-TMI) constitutes an agent bearing the minimum potent pharmacophore of the duocarmycin alkylation subunit and the common pharmacophore of the duocarmycin/CC-1065 alkylation subunits.

Two independent efforts have disclosed the isolation, structure determination, and preliminary evaluation of a new class of antitumor antibiotics now including duocarmycin A[2-4] (**2**), duocarmycin B_1 and B_2 (**3–4**),[6] duocarmycin C_1[3-5] (**5**, pyrindamycin B[7]), and duocarmycin C_2[3] (**6**, pyrindamycin A[7]).[8] The structural similarities between the

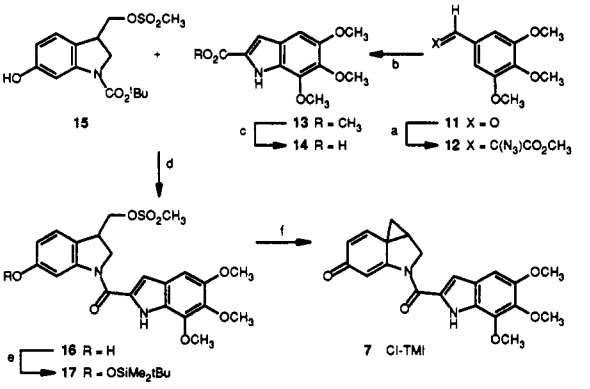


duocarmycins and (+)-CC-1065 (**1**)[9-12] suggest that the agents may be acting by a common or related mechanism initiated with the irreversible covalent alkylation of DNA. Herein, we report the preparation of **7** (CI-TMI) incorporating the parent 1,2,7,7a-tetrahydrocycloprop[1,2-*c*]-indol-4-one (CI) left-hand subunit of the duocarmycins and detail preliminary comparative DNA binding properties for duocarmycin A (**2**), (+)-CC-1065 (**1**), and **7** that provides support for the potential that the agents may be acting by a common mechanism derived from the irre-

Scheme I



Scheme II[a]



[a] (a) 10 equiv of $N_3CH_2CO_2CH_3$, 8 equiv of $NaOCH_3$, MeOH, 0 °C, 5 h, 98%; (b) 140 °C, xylenes, 4 h, 75%; (c) 3.4 equiv of LiOH, THF–MeOH–DMSO–H_2O (3:1:1:1), 23 °C, 18 h, 100%; (d) 3 N HCl/EtOAc, 24 °C, 30 min; 1 equiv of **14**, 3 equiv of EDCI, DMF, 24 °C, 19 h, 77%; (e) 2 equiv of TBDMSCl, 2.5 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2–DMF (5:1), 24 °C, 15 h, 89%; (f) For **17**: 0.9 equiv of $(nBu)_4NF$, THF, 24 °C, 30 min, 61%. For **16**: 1.5 equiv of NaH, THF–DMF (2:1), 0 °C, 2 h, 10–40%.

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(4) DC89-A1 (duocarmycin C_1) and DC88-A (duocarmycin A): Nakano, H.; Takahashi, I.; Ichimura, M.; Kawamoto, I.; Asano, K.; Tomita, F.; Sano, H.; Yasuzawa, T.; Morimoto, M.; Fujimoto, K. PCT. Int. Appl. WO87 06265; *Chem. Abstr.* **1988**, *108*, 110858s.
(5) DC89-A1: Ichimura, M.; Muroi, K.; Asano, K.; Kawamoto, I.; Tomita, F.; Morimoto, M.; Nakano, H. *J. Antibiot.* **1988**, *41*, 1285.
(6) Duocarmycin B_1 and B_2: Ogawa, T.; Ichimura, M.; Katsumata, S.; Morimoto, M.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1299.
(7) (a) Pyrindamycin A and B: Ohba, K.; Watabe, H.; Sasaki, T.; Takeuchi, Y.; Kodama, Y.; Nakazawa, T.; Yamamoto, H.; Shomura, T.; Sezaki, M.; Kondo, S. *J. Antibiot.* **1988**, *41*, 1515. (b) Ishii, S.; Nagasawa, M.; Kariya, Y.; Yamamoto, H.; Inouye, S.; Kondo, S. *J. Antibiot.* **1989**, *42*, 1713. (c) Ohba, K.; Watabe, H.; Nagasawa, M.; Sakakibara, S.; Shomura, T.; Sezaki, M.; Kondo, S. Eur. Pat. Appl. EP 318056; *Chem. Abstr.* **1990**, *112*, 117334j.
(8) The absolute configuration of **2–6** represented herein is derived from that unambiguously established for pyrindamycin A (**6**)[7] by X-ray analysis and assumed for **2–5** based on a presumed common biosynthetic origin. The indistinguishable selectivity of the DNA covalent alkylation profiles of **2**, **5–6** (not shown) is consistent with this representation of the absolute configuration of **2**.
(9) Warpehoski, M. A.; Hurley, L. H. *Chem. Res. Toxicol.* **1988**, *1*, 315.
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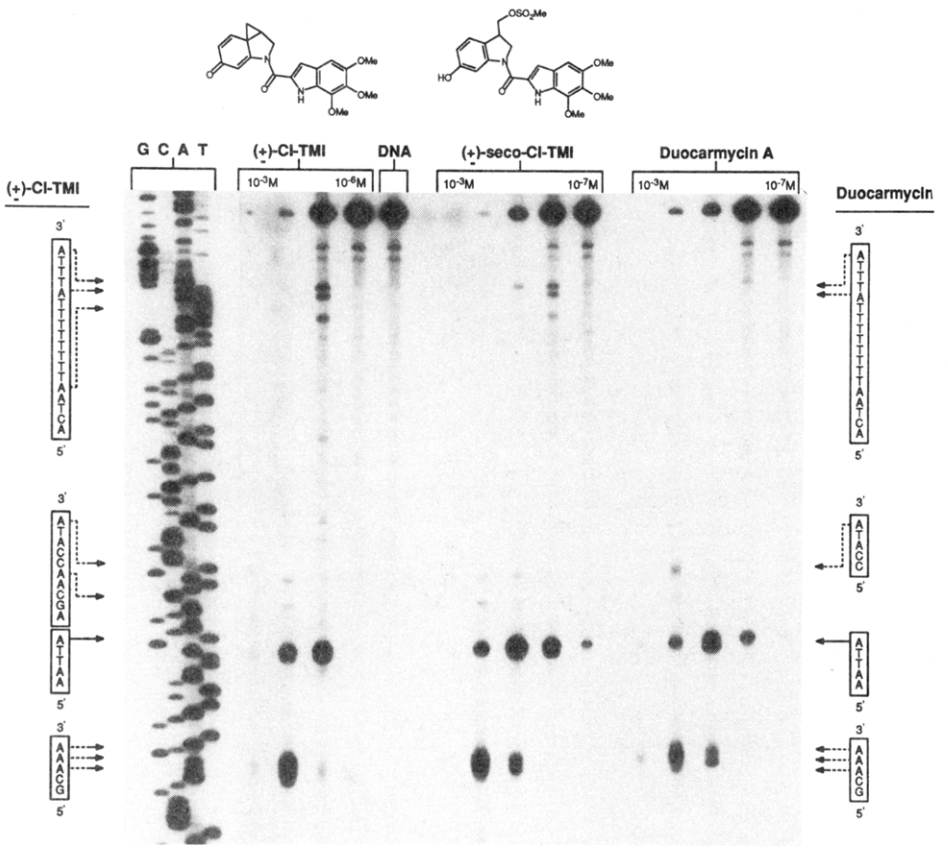

Figure 1. Thermally induced strand cleavage of double-stranded DNA (SV40 DNA fragment, 144 b.p.; nucleotide no. 5238-138, clone w794) after 24 h incubation of agent–DNA at 4 °C followed by removal of unbound agent and 30 min incubation at 100 °C; 8% denaturing poly(acrylamide) gel and autoradiography. Lanes 1–4, Sanger G, C, A, and T reactions; lanes 5–8, (±)-CI-TMI (**7**, 1×10^{-3} to 1×10^{-6} M); lane 9, control DNA; lanes 10–14, (±)-seco-CI-TMI (**16**, 1×10^{-3} to 1×10^{-7} M); lanes 15–19, duocarmycin A (**2**, 1×10^{-3} to 1×10^{-7} M).

versible covalent alkylation of DNA. The results of the comparative studies suggest that **7** (CI-TMI) constitutes an agent bearing the minimum potent pharmacophore of the duocarmycin alkylation subunit *and* the common duocarmycin/CC-1065 alkylation pharmacophore.

The prohibitive reactivity of CI derivatives such as **8**[13] along with the recognition that CI itself would not be expected to couple productively with activated derivatives of carboxylic acids including those of 5,6,7-trimethoxyindole-2-carboxylic acid (**14**) suggested that the final step in the preparation of **7** would optimally involve introduction of the reactive cyclopropane. Consequently, the approach employed in the preparation of **7** was based on a final intramolecular Winstein Ar-3′ alkylation[12] of an appropriately C-3 functionalized 3-methyl-6-hydroxyindoline, e.g. **16**, which in turn was anticipated to be derived from pentultimate coupling of readily available **15**[13] with 5,6,7-trimethoxyindole-2-carboxylic acid (**14**). Acid-catalyzed deprotection of **15** (3 N HCl/EtOAc, 95–100%) followed by immediate coupling of the unstable indoline hydrochloride with 5,6,7-trimethoxyindole-2-carboxylic acid (**14**)[14] provided **16** (77%) (Scheme II). Initial attempts to promote the Ar-3′ alkylation directly on mesylate **16** with closure to the cyclopropane employing a range of reaction conditions (NaH, THF–DMF, 25 °C, 10–40%; Et_3N, THF; DBU, CH_3CN; $NaHCO_3$, THF–H_2O) provided only modest conversions to **7**. Optimal conversion of **16** to **7** was achieved by first conversion of **16** to the phenol *tert*-butyldimethylsilyl ether **17** (tBuMe$_2$SiCl, Et_3N, CH_2Cl_2–DMF, 89%) followed by fluoride-induced silyl ether deprotection of **17** under dilute reaction conditions (0.005 M) with clean phenoxide generation and subsequent in situ closure to **7**. By employing this procedure[15] and chromatographic purification on triethylamine-deactivated silica gel, CI-TMI (**7**) was obtained routinely in yields ≥60%.[16]

Having established in prior studies that derivatives of CI display characteristics consistent with its assignment as the pharmacophore of the CC-1065 alkylation subunit,[17] we sought to establish whether CI may constitute the pharmacophore of duocarmycin alkylation subunit and, as such, constitute the common pharmacophore relating

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(14) The preparation of **14** (supplementary material) was carried out by the general experimental procedure detailed in Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1775.

(15) Saunders, D. G. *Synthesis* **1988**, 377.

(16) For the initial disclosure of the use of the Winstein Ar-3′ alkylation (see: Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 4238. Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 567) for the preparation of *N*-sulfonyl derivatives of CPI, see: Wierenga, W. *J. Am. Chem.* Soc. **1981**, *103*, 5621. For additional studies on the synthesis of the CPI left-hand subunit of CC-1065, see ref 12 and references cited therein. For studies that include simplified or modified left-hand subunits, see: ref 13. (a) Boger, D. L.; Ishizaki, T.; Wysocki, R. J., Jr.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461. Boger, D. L.; Ishizaki, T. *Tetrahedron Lett.* **1990**, *31*, 793. (b) Alternative CI synthesis: Drost, K. J.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1989**, *54*, 5985. (c) Sundberg, R. J.; Nishiguchi, T. *Tetrahedron Lett.* **1983**, *24*, 4773. Sundberg, R. J.; Baxter, E. W. *Tetrahedron Lett.* **1986**, *27*, 2687. Sundberg, R. J.; Baxter, E. W.; Pitts, W. J.; Ahmed-Schofield, R.; Nishiguchi, T. *J. Org. Chem.* **1988**, *53*, 5097. (d) Bryson, T. A.; Roth, G. A. *Tetdrahedron Lett.* **1988**, *29*, 2167. Bryson, T. A.; Roth, G. A.; Jing-hau, L. *Tetrahedron Lett.* **1986**, *27*, 3685.

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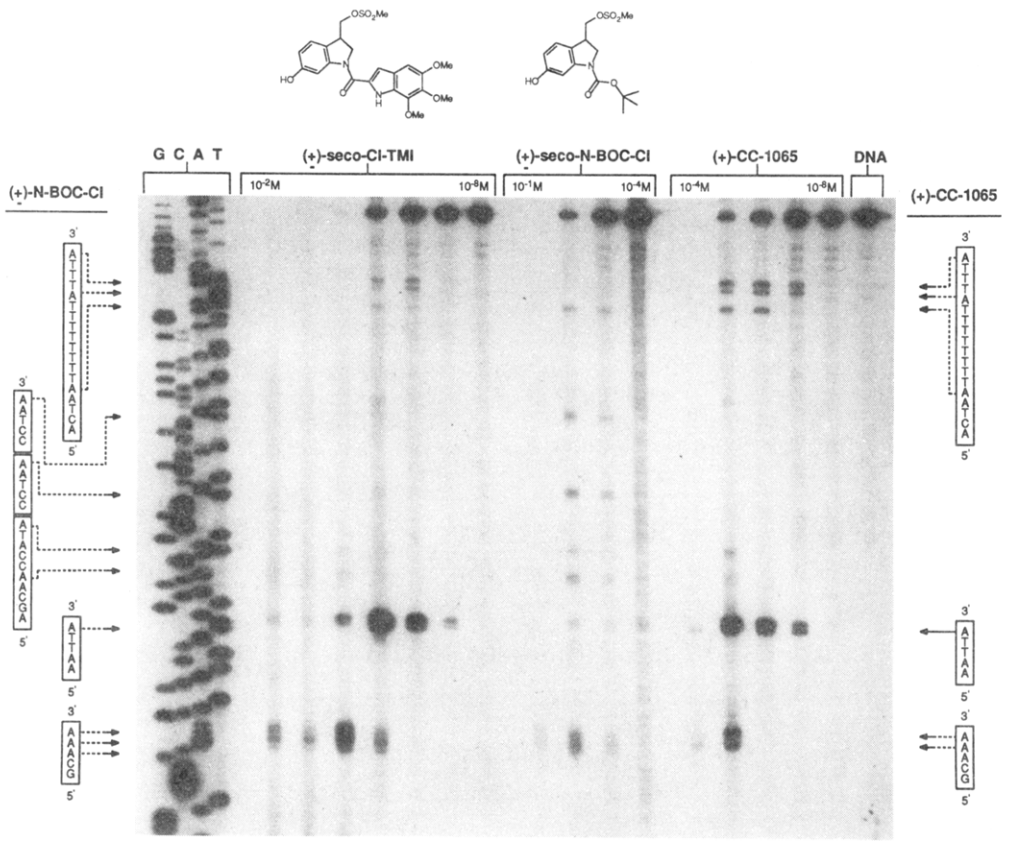

Figure 2. Thermally induced strand cleavage of double-strand DNA (SV40 DNA fragment, 144 b.p.; nucleotide no. 5238-138, clone w794) after 24 h incubation of agent–DNA at 4 °C followed by removal of unbound agent and 30 min incubation at 100 °C; 8% denaturing poly(acrylamide) gel and autoradiography. Lanes 1–4, Sanger, G, C, A, and T reactions; lanes 5–11; (±)-seco-CI-TMI (**16**, 1×10^{-2} to 1×10^{-8} M); lanes 12–15, (±)-seco-*N*-BOC-CI (**15**, 1×10^{-1} to 1×10^{-4} M), identical with (±)-*N*-BOC-CI (**8**, not shown);[17] lanes 16–20, (+)-CC-1065 (**1**, 1×10^{-4} to 1×10^{-8} M); lane 21, control DNA.

Table I. In Vitro Cytotoxic Activity IC_{50} (μg/mL)[a]

agent	configuration	L1210
1, (+)-CC-1065	natural	0.00001
2, duocarmycin A	natural	0.00002
16, *seco*-CI-TMI	–	0.0002
7, CI-TMI	–	0.001
8, (±)-*N*-BOC-CI	–	10
9, (+)-*N*-BOC-CPI	natural	0.1
15, (±)-**15**	–	0.2

[a] The cell culture cytotoxicity assays were performed as described: Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918. IC_{50}, inhibitory concentration for 50% cell growth relative to untreated controls. L1210, mouse lymphocytic leukemia cell culture.

the CC-1065 and duocarmycin natural products. Table I details the results of the in vitro cytotoxic evaluation of (+)-CC-1065 (**1**), duocarmycin A (**2**), (±)-CI-TMI (**7**), **8–9**, and **15–16**, and the cytotoxic potency of the agents proved consistent with trends exhibited in the relative intensity and selectivity of the agent DNA covalent alkylation.

The demonstration of the event, site, and relative selectivity of the DNA covalent alkylation of the agents (**1–2**, **15–16**) was obtained from the thermally induced strand cleavage of double-stranded DNA after exposure to the agents (covalent alkylation, autofootprinting).[9,17–21] The DNA covalent alkylation of (+)-CC-1065 (**1**) and that proposed for duocarmycin A (**2**) were examined within four clones of M13mp10 harboring SV40 nucleosomal DNA. Thus, employing the four singly 5′-^{32}P-end-labeled SV40 double-stranded DNA fragments derived from clones w794, w836, c988, and c820,[22] a range of concentrations of the agents was incubated with the labeled DNA (24 h, 4 °C), unbound agent was removed by ethanol precipitation of the DNA, and a solution containing the agent–DNA covalent complexes was warmed at 100 °C (30 min) to induce strand cleavage at the sites of covalent alkylation.[18,19] Electrophoresis of the resulting DNA under denaturing conditions alongside Sanger dideoxynucleotide sequencing reactions followed by autoradiography permitted the identification of the sites of DNA covalent alkylation.[23]

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(23) In these studies, we have shown that the sequence-selectivity of the DNA covalent alkylation of duocarmycin A = duocarmycin C_2 = duocarmycin C_1 [three base-pair binding selectivity = 5′-(AA*A*)-3′ > 5′-(TT*A*)-3′ > 5′-(TA*A*)-3′ > 5′-(AT*A*)-3′; fourth base-pair sensitivity = 5′-(A/TXX*A*)-3′ ≫ 5′-(G/CXX*A*)-3′; preceding base-pair sensitivity = 5′-(NXX*A*Pu)-3′ > 5′-(NXX*A*Py)-3′; high affinity consensus sequences = 5′-(A/TAA*A*)-3′ and 5′-(A/TTT*A*)-3′] and that the relative intensity of DNA covalent alkylation (4 °C, 24 h) is duocarmycin A ≥ duocarmycin C_2 (ca. 1–10×) > duocarmycin C_1 (ca. 10–100×) and (37 °C, 24 h) $C_1 \cong C_2 >$ A (5–10×). Moreover, in these studies we have demonstrated that (±)-*N*-BOC-CI (**8**, as well as (+)- and (−)-*N*-BOC-CI) exhibit a DNA covalent alkylation profile that is remarkably similar to that of (+)-*N*-BOC-CPI (**9**, identical sites but less selectivity among the available sites, see Figure 2) that is quite distinct from the DNA covalent alkylation profile of (+)-CC-1065 (Figure 2).[20] We attribute this increased covalent alkylation selectivity of even the exceptionally reactive electrophile of **7** to a prominent noncovalent binding selectivity of the agents preferentially within the narrower, sterically more accessible A-T rich minor groove effectively restricting the number of available alkylation sites.[12,17,20]

(±)-CI-TMI (7) and (±)-*seco*-CI-TMI (16) displayed a DNA covalent alkylation profile strikingly similar to that of duocarmycin A (Figure 1), substantially more selective than racemic (±)-*N*-BOC-CI (Figure 2) or optically active (+)- and (−)-*N*-BOC-CI[17,23] (not shown), and remarkably similar to that of (+)-CC-1065 (Figure 2). The selectivity of the covalent alkylation of 7 (CI-TMI) and 16 (*seco*-CI-TMI) proved virtually indistinguishable, and the intensity of the DNA alkylation exhibited by 16 proved comparable to that of duocarmycin A but greater than that of 7 (CI-TMI, ca. 10–100×). Presumably this may be attributed to the relative instability of 7 to the conditions of assay.[13]

Selectivity: duocarmycin A ≅ (±)-CI-TMI (7) = (±)-16 ≫ (±)-*N*-BOC-CI (8) = (±)-15. Intensity: (+)-CC-1065 (ca. 1–0.1×) ≥ duocarmycin A ≅ (±)-16 (ca. 1–10×) ≥ (±)-CI-TMI (7, ca. 10–100×) ≫ (±)-15 (ca. 10^3–10^4×) ≅ (±)-*N*-BOC-CI (8, ca. 10^4×).

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Supplementary Material Available: Full experimental details for the preparation of 14, 16–17, and 7 and a summary of the DNA binding studies (6 pages). Ordering information is given on any current masthead page.

Reaction of Bicyclo[6.3.0]undeca-2,4,6,8,11-pentaen-10-ylidene in Oxygen-Doped Matrices: Characterization of the First Carbonyl Oxide with a π-Donating Ring System†

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Summary: The first carbonyl oxide with a π-donating ring system, which is generated by the reaction of the title carbene with O_2 in an Ar matrix, exhibits a considerably long wavelength UV absorption and remarkable photochemical stability.

Carbonyl oxides are established as reactive intermediates in many oxidation reactions. In recent years, carbonyl oxides have been characterized spectroscopically by the use of the matrix isolation technique[1,2] and laser flash photolysis.[3] However, the studies have been limited to carbonyl oxides with aryl groups or π-accepting ring systems, all of which have the UV–vis absorption maxima in the range of 380–460 nm. Recent semiempirical calculations suggested that strong π-electron donors cause significant perturbation to properties of the parent carbonyl oxide: an increase of zwitterionic character, an increase of nucleophilicity, and a considerable red shift of the π→π* transition maximum.[4] In this paper we report the spectroscopic characterization of the carbonyl oxide formed from the title carbene (1) in O_2-doped Ar matrix. This is the first direct observation of a carbonyl oxide with a π-electron-donating ring system,[5] revealing the validity of theoretical predictions on this class of carbonyl oxides.

Photolysis (λ > 350 nm, 1 h) of the 10-diazobicyclo[6.3.0]undeca-2,4,6,8,11-pentaene (2)[6] matrix isolated in Ar at 12 K afforded the title carbene 1, which showed IR absorptions at 800 and 687 cm^{-1}. The matrix containing 1 had a light red color, the UV–vis spectrum of which showed absorption with maxima at 546 and 506 nm. The characterization of 1 was confirmed by the ESR measurement. Irradiation of 2 in 2-methyltetrahydrofuran at 17 K gave intense signals characteristic of a triplet species, the zero-field splitting parameters of which were evaluated to be D = 0.2401 cm^{-1} and E = 0.0044 cm^{-1}. The spec-

Table I. IR Data of Carbonyl Oxide 3 Matrix-Isolated in Ar at 12 K

3	$^{18}O_2$–3	Δ[a]
1463 (m)	1462 (m)	1
1417 (w)	1415 (w)	2
1406 (m)	1405 (m)	1
1369 (m)	1362 (w)	7
1326 (m)	1325 (w)	1
1132 (m)	1124 (m)	8
971 (s)	961 (m)	10
931 (s)	889 (s), 882 (s)	42, 49
905 (m)	*b*	–
849 (w)	845 (m)	4
842 (m)	838 (m)	4
700 (w)	699 (w)	1
692 (w)	680 (w)	12

[a] ^{18}O isotopic shifts in cm^{-1}. [b] This peak cannot be assigned, probably due to overlapping with strong peaks.

† This work is respectfully dedicated to Professor W. Kirmse on the occasion of his 60th birthday.

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