

Kiyoshi Matsumoto*, Naoto Hayashi, Yukio Ikemi and Mitsuo Toda†

Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, 606-8501, Japan

Takane Uchida, Kinuyo Aoyama and Yoshihiro Miyakoshi

Faculty of Education, Fukui University, Fukui 910-8507, Japan

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Dedicated to the memory of Professor Raymond N. Castle

Cyclooctyne underwent 1,3-dipolar cycloaddition with pyridinium bis(methoxy-carbonyl)methylides to afford the corresponding indolizines (8-methoxycarbonyl-7-azatricyclo[7.6.0.0^{2,7}]pentadeca-1,3,5,8-tetraenes) in good to moderate yields. Some molecular orbital considerations are also described on this reaction compared with the results on the reaction of pyridinium dicyanomethylides with cyclooctyne.

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Cyclooctyne is the smallest cyclic alkyne that is stable at room temperature and has been prepared by a number of methods that either start from cyclooctene or from cyclooctanone [1-5]. Usually, 1,3-dipolar cycloaddition reactions (HOMO-LUMO controlled) of dipoles with non-activated alkynes and alkenes proceed either sluggishly or fail [6]. In spite of the high strain and high reactivity of cyclooctyne as well as the synthetic potential of its cycloadditions, only few examples of 1,3-dipolar cycloaddition reactions have

been reported [7,8]. Previously we investigated 1,3-dipolar cycloadditions by reacting pyridinium dicyanomethylides with cyclopropene [9], and with alkyne and related equivalent structures. [10] We also studied the regioselectivity of unsymmetric pyridinium dicyanomethylides with dimethyl acetylenedicarboxylate and methyl propanoate in 1,3-dipolar cycloaddition reactions [11]. We have also investigated substituent effects on ¹³C and ¹⁵N-NMR chemical shifts of the ylidic carbons and nitrogens of 4-substituted

Table 1
8-Methoxycarbonyl-7-azatricyclo[7.6.0.0^{2,7}]pentadeca-1,3,5,8-tetraene **3**

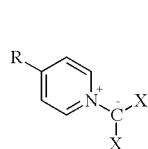
Compound	R	React. Mol. Ratio ^[a]	Condition React. Time ^[b] (h)	Mp (°C)	Yield (%)	IR (cm ⁻¹ ; KBr disk)	MS (m/z)	Formula	Elemental Analysis (%)		
									Calcd.	Found	N
3a	H	1.4	9	82.0-83.1	62	1665	257(M ⁺), 198	C ₁₆ H ₁₉ NO ₂	74.69	7.44	5.44
									74.54	7.34	5.44
3b	CH ₃	1.8	1	82.0-83.2	41	1660	271(M ⁺), 243, 212	C ₁₇ H ₂₁ NO ₂	75.25	7.80	5.16
									74.97	7.84	5.00
3c	CH ₂ CH ₃	1.8	1.5	57.0-61.0	32	1670	285(M ⁺)	C ₁₈ H ₂₃ NO ₂	75.76	8.12	4.91
									74.67	8.07	4.82
3d	CH ₂ CH ₂ CH ₃	2	1.5	66.0-69.0	15	1660	299(M ⁺)	C ₁₉ H ₂₅ NO ₂	76.22	8.42	4.68
									76.10	8.37	4.40
3e	CH(CH ₃) ₂	2	12	syrup	53	1670 [c]	299(M ⁺)	C ₁₉ H ₂₅ NO ₂	76.22	8.42	4.68
									75.97	8.39	4.61
3f	C(CH ₃) ₃	2	6	111.5-112.0	48	1670 [c]	313(M ⁺)	C ₂₀ H ₂₇ NO ₂	76.64	8.68	4.47
									76.45	8.56	4.17
3g	C ₆ H ₅	1.2	2	166.0-167.5	48	1670	333(M ⁺)	C ₂₂ H ₂₃ NO ₂	79.25	6.95	4.20
									79.18	6.99	4.17
3h	COCH ₃	1.3	2	173.0-173.8	66	1670	299(M ⁺), 271, 240	C ₁₈ H ₂₁ NO ₃	72.22	7.07	4.68
									72.09	7.08	4.46
3i	COC ₆ H ₅	2	6	132.5-132.9	97	1680, 1645	361(M ⁺)	C ₂₃ H ₂₃ NO ₃	76.43	6.41	3.88
									76.26	6.52	3.78
3j	CN	1.5	1	169.5-170.0	48	1680, 2200	282(M ⁺), 223	C ₁₇ H ₁₈ N ₂ O ₂	72.32	6.43	9.92
									72.18	6.44	9.79
3k	di-CH ₃	1.5	24	88.0-89.0	13	1665	285(M ⁺)	C ₁₈ H ₂₃ NO ₂	75.76	8.12	4.91
									75.49	8.22	4.88
3l	isoquinolinium	1.3	24	133.5-134.5	67	1675	307(M ⁺)	C ₂₀ H ₂₂ NO ₂	78.15	6.88	4.56
									77.87	6.94	4.27

[a] Mol. ratio of cyclooctyne **3** and ylide **1**; [b] Reflux in toluene; [c] Liquid film.

Table 2
¹H-NMR Data of 8-methoxycarbonyl-7-azatricyclo[7.6.0.0^{2,7}]pentadeca-1,3,5,8-tetraene **3**

Compound	R	pmr (δ : CDCl ₃)
3a	H	1.25-1.32, 1.44-1.48, 1.59-1.62, 1.70-1.75 (each m, 8H, H-11, 12, 13, 14), 2.81, 3.09 (each dd, J = 5.0, 5.0 Hz, 4H, H-10, 15), 3.09 (s, 3H, OCH ₃), 6.67 (dd, J = 10.0, 5.0 Hz, 1H, H-5), 6.94 (dd, J = 5.0, 5.0 Hz, 1H, H-4), 7.37 (d, J = 5.0 Hz, 1H, H-3), 9.44 (d, J = 10.0 Hz, 1H, H-6)
3b	CH ₃	1.25-1.30, 1.43-1.48, 1.58-1.63, 1.69-1.74 (each m, 2H, H-11, 12, 13, 14), 2.34 (s, 3H, CH ₃), 2.78, 3.07 (each dd, J = 6.1, 6.1 Hz, 2H, H-10, 15), 3.91 (s, 3H, OCH ₃), 6.51 (dd, J = 7.3, 1.8 Hz, 1H, H-5), 7.12 (s, 1H, H-3), 9.33 (d, J = 7.3 Hz, 1H, H-6)
3c	CH ₂ CH ₃	1.24-1.30, 1.43-1.47, 1.58-1.63, 1.68-1.73 (each m, 8H, H-11, 12, 13, 14), 1.26 (t, J = 7.3 Hz, 3H, Et-CH ₃), 2.63 (q, J = 7.3 Hz, 2H, Et-CH ₂), 2.78, 3.06 (each dd, J = 6.1, 6.1 Hz, 2H, H-10, 15), 3.88 (s, 3H, OCH ₃), 6.54 (dd, J = 7.3, 1.8 Hz, 1H, H-5), 7.11 (s, 1H, H-3), 9.35 (d, J = 7.3 Hz, 1H, H-6)
3d	CH ₂ CH ₂ CH ₃	0.96 (t, J = 7.3 Hz, 3H, Pr-CH ₃), 1.26-1.31, 1.44-1.48, (each m, 4H, H-11, 14), 1.59-1.74 (m, 6H, H-12, 13, Pr-CH ₂), 2.57 (t, J = 7.6 Hz, 2H, Pr-CH ₂), 2.78, 3.07 (each dd, J = 6.1, 6.1 Hz, 4H, H-10, 15), 3.89 (s, 3H, OCH ₃), 6.54 (dd, J = 7.3, 1.8 Hz, 1H, H-5), 7.11 (s, 1H, H-3), 9.35 (d, J = 7.3 Hz, 1H, H-6)
3e	CH (CH ₃) ₂	1.23-1.36 (m, 2H, H-11), 1.27 (d, J = 6.9 Hz, 6H, Pr-CH ₃), 1.42-1.53 (m, 2H, H-14), 1.57-1.82 (m, 4H, H-12, 13), 2.80 (dd, J = 5.9, 5.9 Hz, 2H, H-15), 2.89 (t, J = 6.9 Hz, 1H, Pr-CH), 3.07 (dd, J = 6.3, 6.3 Hz, 2H, H-10), 3.89 (s, 3H, OCH ₃), 6.60 (dd, J = 7.2, 2.0 Hz, 1H, H-5), 7.14 (s, 1H, H-3), 9.36 (d, J = 7.2 Hz, 1H, H-6)
3f	C (CH ₃) ₃	1.18-1.53 (m, 4H, H-11, 12), 1.34 (s, 9H, Bu-CH ₃), 1.56-1.82 (m, 4H, H-12, 13), 2.81 (dd, J = 5.9, 5.9 Hz, 2H, H-15), 3.07 (dd, J = 6.5, 6.5 Hz, 2H, H-10), 3.89 (s, 3H, OCH ₃), 6.74 (dd, J = 7.5, 2.3 Hz, 1H, H-5), 7.22 (s, 1H, H-3), 9.34 (d, J = 7.5 Hz, 1H, H-6)
3g	C ₆ H ₅	1.28-1.33, 1.46-1.51, 1.63-1.68, 1.72-1.77 (each m, 8H, H-11, 12, 13, 14), 2.87, 3.11 (each dd, 6.1, 6.1 Hz, 4H, H-10, 15), 3.92 (s, 3H, OCH ₃), 6.99 (ABq, J = 7.3, 1.8 Hz, 1H, H-5), 7.36 (dd, J = 7.3, 7.3 Hz, 1H, Ph-H), 7.46 (dd, J = 7.9, 7.3 Hz, 2H, Ph-H), 7.57 (d, J = 1.8 Hz, 1H, H-3), 7.67 (d, J = 7.9 Hz, 2H, Ph-H), 9.48 (d, J = 7.3 Hz, 1H, H-6)
3h	COCH ₃	1.25-1.30, 1.46-1.59, 1.64-1.69, 1.71-1.76 (each m, 8H, H-11, 12, 13, 14), 2.62 (s, 3H, OCH ₃), 2.89, 3.09 (each dd, J = 6.1, 6.1 Hz, 4H, H-10, 15), 3.94 (s, 3H, OCH ₃), 7.19 (dd, J = 7.7, 1.8 Hz, 1H, H-5), 8.00 (d, J = 1.8 Hz, 1H, H-3), 9.38 (d, J = 7.7 Hz, 1H, H-6)
3i	COC ₆ H ₅	1.10-1.87 (m, 8H, H-11, 12, 13, 14), 2.83 (dd, J = 5.9, 5.9 Hz, 2H, H-15), 3.11 (dd, J = 6.3, 6.3 Hz, 2H, H-10), 3.95 (s, 3H, OCH ₃), 7.17 (dd, J = 7.4, 1.8 Hz, 1H, H-5), 7.46-7.66 (m, 3H, Ph-H), 7.81 (d, J = 8.1 Hz, 2H, Ph-H), 7.88 (s, 1H, H-3), 9.44 (d, J = 7.4 Hz, 1H, H-6)
3j	CN	1.23-1.29, 1.45-1.49, 1.62-1.67, 1.71-1.76 (each m, 8H, H-11, 12, 13, 14), 2.83 (dd, J = 6.1, 6.1 Hz, 2H, H-15), 3.09 (dd, J = 6.4, 6.4 Hz, 2H, H-10), 3.95 (s, 3H, OCH ₃), 6.73 (dd, J = 7.3, 1.8 Hz, 1H, H-5), 7.77 (d, J = 1.8 Hz, 1H, H-3), 9.42 (d, J = 7.3 Hz, 1H, H-6)
3k	di-CH ₃	1.28-1.42, 1.58-1.73 (each m, 8H, H-11, 12, 13, 14), 2.24 (s, 3H, CH ₃), 2.58 (s, 3H, CH ₃), 2.97, 3.05 (each dd, J = 6.1, 6.1 Hz, 4H, H-10, 15), 3.89 (s, 3H, OCH ₃), 6.54 (s, 1H, H-4), 9.25 (s, 1H, H-6)
3l	isoquinolinium	1.37-1.48, 1.66-1.88 (each m, 8H, H-11, 12, 13, 14), 3.12, 3.16 (each dd, J = 6.1, 6.1 Hz, 4H, H-10, 15), 3.92 (s, 3H, OCH ₃), 6.84 (d, J = 7.3 Hz, 1H, H-5), 7.39-7.53 (m, 2H, Ar-H), 7.61 (d, J = 7.9 Hz, 1H, Ar-H), 8.32 (d, J = 8.6 Hz, 1H, Ar-H), 9.27 (d, J = 7.3 Hz, 1H, H-6)

Scheme



1: X = CO₂CH₃

4: X = CN

a: R = H

b: R = CH₃

c: R = CH₂CH₃

d: R = CH₂CH₂CH₃

e: R = CH(CH₃)₂

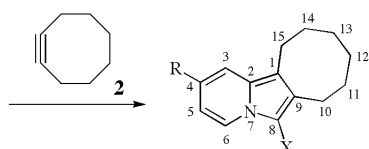
f: R = C(CH₃)₃

g: R = C₆H₅

h: R = COCH₃

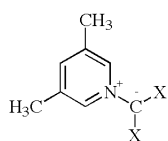
i: R = COC₆H₅

j: R = CN



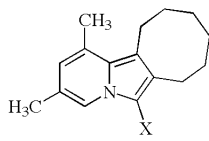
3: X = CO₂CH₃

5: X = CN



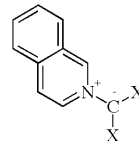
1k: X = CO₂CH₃

4k: X = CN



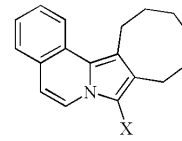
3k: X = CO₂CH₃

5k: X = CN



1l: X = CO₂CH₃

4l: X = CN



3l: X = CO₂CH₃

5l: X = CN

Table 3
¹³C NMR Data of 8-Methoxycarbonyl-7-azatricyclo[7.6.0.0.2⁷]pentadeca-1,3,5,8-tetraene **3**

Compound	R	C=O	CH ₃ O	C-1	C-2	C-3	C-4	cmr (δ:CDCl ₃)						R	
								C-5	C-6	C-8	C-9	C-10 C-15	C-11 C-14		C-12 C-13
3a	H	162.74	50.61	115.75	136.65	115.80	120.88	111.51	127.74	110.21	134.66	22.81	30.12	25.65	
3b	CH ₃	162.70	50.49	114.48	137.01	114.35	131.56	114.11	127.25	109.53	135.11	22.75	30.16	25.68	21.14
3c	CH ₂ CH ₃	162.60	50.38	114.62	137.62	112.93	136.90	112.75	127.36	109.44	135.06	22.69	30.06	25.57	28.24, 14.45
3d	(CH ₂) ₂ CH ₃	162.70	50.49	114.66	136.99	113.73	136.23	113.35	127.38	109.52	135.11	22.78	30.16	25.66	37.48,
3e	CH(CH ₃) ₂	162.66	50.44	114.83	136.95	111.64	142.25	111.34	127.55	109.45	135.06	22.75	30.08	25.59	23.59, 13.77
3f	C(CH ₃) ₃	162.62	50.41	115.08	136.87	110.76	144.56	109.99	127.24	109.34	134.83	22.70	30.08	25.55	34.43, 30.46
3g	C ₆ H ₅	162.68	50.65	116.57	137.29	112.70	134.89	111.02	127.78	110.15	133.53	22.86	30.10	25.64	136.22, 128.92,
3h	COCH ₃	162.47	51.06	113.07	137.25	118.02	128.75	121.00	126.95	109.07	132.84	22.98	29.97	25.61	127.69, 126.5
3i	COC ₆ H ₅	162.48	51.06	112.90	137.70	120.85	137.30	120.20	126.90	110.94	128.70	22.90	29.98	25.57	195.95, 26.14
3j	CN	162.31	51.28	120.24	137.81	118.61	127.73	102.77	122.45	110.78	131.95	22.87	29.92	25.57	194.50, 132.70,
3k	di-CH ₃	162.82	50.52	115.92	136.92	126.87	123.80	120.36	125.54	109.89	133.24	23.39	30.60	26.17	132.20, 129.65,
3l	isoquino- linium	162.83	50.88	137.25	137.25	128.91	126.00	111.11	127.05	111.93	129.72	24.02	29.33	26.26	128.37
												24.31	30.98	26.32	113.57

Table 4

HOMO and LUMO Energies (eV) of Pyridinium Bis(methoxycarbonyl)methylides **1** and Cyclooctyne **2** and Energy Differences (eV) of LUMO (Cyclooctyne)-HOMO (Ylide) and LUMO (Ylide)-HOMO (Cyclooctyne)

Ylide	INDO				AM1				PM3			
	HOMO	L (C)-H (Y)	LUMO	L (Y)-H (C)	HOMO	L (C)-H (Y)	LUMO	L (Y)-H (C)	HOMO	L (C)-H (Y)	LUMO	L (Y)-H (C)
1a	-5.191	15.432	4.846	12.485	-8.383	9.825	-1.202	8.786	-8.595	9.765	-0.995	9.157
1b	-4.950	15.191	4.931	12.570	-8.320	9.762	-1.244	8.744	-8.471	9.641	-0.994	9.158
1c	-4.930	15.171	4.935	12.574	-8.317	9.759	-1.231	8.757	-8.455	9.625	-0.978	9.174
1d	-4.911	15.152	4.959	12.598	-8.298	9.740	-1.201	8.787	-8.482	9.652	-0.993	9.159
1e	-4.890	15.131	5.020	12.659	-8.214	9.656	-1.081	8.907	-8.481	9.651	-0.971	9.181
1f	-4.868	15.109	5.028	12.667	-8.258	9.700	-1.118	8.870	-8.464	9.634	-0.969	9.183
1g	-4.939	15.180	4.448	12.087	-8.258	9.700	-1.399	8.589	-8.391	9.561	-1.305	8.847
1h	-5.263	15.504	3.792	11.431	-8.584	10.026	-1.724	8.264	-8.797	9.967	-1.470	8.682
1i	-5.265	15.506	3.743	11.382	-8.513	9.955	-1.673	8.315	-8.777	9.947	-1.463	8.689
1j	-5.365	15.606	3.890	11.529	-8.671	10.113	-1.798	8.190	-8.913	10.083	-1.643	8.509
1k	-5.073	15.314	5.054	12.693	-8.319	9.761	-1.104	8.884	-8.492	9.662	-0.865	9.287
1l	-5.010	15.251	4.300	11.939	-8.245	9.687	-1.465	8.523	-8.407	9.577	-1.380	8.772
Cyclooctyne 2	(LUMO) 10.241		(HOMO) -7.639		(LUMO) 1.442		(HOMO) -9.988		(LUMO) 1.170		(HOMO) -10.152	

pyridinium dicyanomethylides and bis(methoxycarbonyl)-methylides [12]. Furthermore, good correlations were found between the ¹³C- and ¹⁵N-NMR chemical shifts and the partial charges obtained by different computational methods (AM1, PM3, MNDO) of some 4-substituted pyridinium dicyanomethylides [13] and bis(methoxy-

carbonyl)methylides [14]. In connection with the recently published results on the reactions of pyridinium dicyanomethylides with cyclooctyne [15], we now describe in full detail the 1,3-dipolar cycloaddition reactions of cyclooctyne **2** with pyridinium bis(methoxycarbonyl)-methylides **1** [16].

Table 5
HOMO and LUMO Energies (eV) of Pyridinium Dicyanomethylides **4** and Cyclooctyne **2** and
Energy Differences (eV) of LUMO (Cyclooctyne)-HOMO (Ylide) and LUMO (Ylide)-HOMO (Cyclooctyne)

Ylide	INDO				AM1				PM3			
	HOMO	L (C)-H (Y)	LUMO	L (Y)-H (C)	HOMO	L (C)-H (Y)	LUMO	L (Y)-H (C)	HOMO	L (C)-H (Y)	LUMO	L (Y)-H (C)
4a	-4.723	14.964	4.856	12.495	-8.283	9.725	-1.301	8.687	-8.653	9.823	-1.473	8.679
4b	-4.440	14.681	4.913	12.552	-8.176	9.618	-1.288	8.700	-8.544	9.714	-1.456	8.696
4c	-4.419	14.660	4.937	12.576	-8.156	9.598	-1.262	8.726	-8.522	9.692	-1.431	8.721
4d	-4.404	14.645	4.958	12.597	-8.152	9.594	-1.259	8.729	-8.520	9.690	-1.431	8.721
4e	-4.366	14.607	5.007	12.646	-8.161	9.603	-1.250	8.738	-8.544	9.714	-1.434	8.718
4f	-4.354	14.595	5.034	12.673	-8.148	9.590	-1.227	8.761	-8.535	9.705	-1.877	8.275
4g	-4.465	14.706	4.296	11.935	-8.117	9.559	-1.577	8.411	-8.463	9.633	-1.697	8.455
4h	-4.874	15.115	3.800	11.439	-8.547	9.989	-1.840	8.148	-8.879	10.049	-1.919	8.233
4i	-4.857	15.098	3.802	11.441	-8.499	9.941	-1.800	8.188	-8.835	10.005	-1.877	8.275
4j	-4.835	15.076	3.931	11.570	-8.650	10.092	-1.948	8.040	-9.001	10.171	-2.092	8.060
4k	-4.552	14.793	5.148	12.787	-8.184	9.626	-1.172	8.816	-8.552	9.722	-1.328	8.824
4l	-4.528	14.769	4.350	11.989	-8.554	9.996	-1.574	8.414	-8.468	9.638	-1.752	8.400
Cyclooctyne (2)	(LUMO)		(HOMO)		(LUMO)		(HOMO)		(LUMO)		(HOMO)	
2	10.241		-7.639		1.442		-9.988		1.170		-10.152	

Table 6
Energy Differences (eV) of LUMO (Ylide **1** and **4**)-HOMO (Cyclooctyne **2**)

Substituent (R)	INDO			AM1			PM3		
	L (Y-1)-H (C)	L (Y-4)-H (C)	D E ^[a]	L (Y-1)-H (C)	L (Y-4)-H (C)	D E ^[a]	L (Y-1)-H (C)	L (Y-4)-H (C)	D E ^[a]
a (H)	12.485	12.495	-0.010	8.786	8.687	0.099	9.157	8.679	0.478
b (CH ₃)	12.570	12.552	0.018	8.744	8.700	0.044	9.158	8.696	0.462
c (CH ₂ CH ₃)	12.574	12.576	-0.002	8.757	8.726	0.031	9.174	8.721	0.453
d (CH ₂ CH ₂ CH ₃)	12.598	12.597	0.001	8.787	8.729	0.058	9.159	8.721	0.438
e (CH (CH ₃) ₂)	12.659	12.646	0.013	8.907	8.738	0.169	9.181	8.718	0.463
f (C (CH ₃) ₃)	12.667	12.673	-0.006	8.870	8.761	0.109	9.183	8.275	0.908
g (C ₆ H ₅)	12.087	11.935	0.152	8.589	8.411	0.178	8.847	8.455	0.392
h (COCH ₃)	11.431	11.439	-0.008	8.264	8.148	0.116	8.682	8.233	0.449
i (COC ₆ H ₅)	11.382	11.441	-0.059	8.315	8.188	0.127	8.689	8.275	0.414
j (CN)	11.529	11.570	-0.041	8.190	8.040	0.150	8.509	8.060	0.449
k (di-CH ₃)	12.693	12.787	-0.094	8.884	8.816	0.068	9.287	8.824	0.463
l (isoq.)	11.939	11.989	-0.050	8.523	8.414	0.109	8.772	8.400	0.372

[a] Differences of pyridinium bis(methoxycarbonyl)methylide **1** and pyridinium dicyanomethylide **4**.

For example, reactions of pyridinium bis(methoxycarbonyl)methylide (**1a**, 2.14 mmol) with cyclooctyne **2** (3.00 mmol) in refluxing toluene for 9 hours gave, after spontaneous dehydrogenation and elimination of acetic acid, 62% yield of the indolizine **3a**. The generality of the reaction is illustrated in Table 1. The yields were good to moderate. The elemental analyses as well as ir, ¹H and ¹³C nmr spectra are in agreement with structure **3** (Tables 1-3).

The values of HOMO and LUMO energy of pyridinium bis(methoxycarbonyl)methylides **1a-n** and cyclooctyne were calculated by semi-empirical molecular orbital calculations such as a PM3 method (CACH) [17]. The results are summarized in Table 4. These results indicate that the reaction proceeds between the LUMO of the 1,3-dipole and the HOMO of cyclooctyne, because the

calculated energy difference between bis(methoxycarbonyl)methylide (LUMO)-cyclooctyne (HOMO) are smaller than those of bis(methoxycarbonyl)methylide (HOMO)-cyclooctyne (LUMO). In agreement with this, pyridinium bis(methoxycarbonyl)methylides **1h**, **1i**, and **1j** having an electron withdrawing group such as benzoyl, acetyl and cyano group (*eg.* their LUMO energies are smaller than -1.43 eV) generally gave the corresponding indolizines **3h-j** in good to moderate yields, whereas pyridinium bis(methoxycarbonyl)methylides **1a-f** usually require a longer reaction time to obtain a moderate yield of the corresponding indolizines **3a-f**. Specifically, 3,5-dimethylpyridinium bis(methoxycarbonyl)methylide **1k** with **2** afforded only 13 % yield of **3k** even after refluxing for 1 day. When comparing the qualitative

experimental observations with values obtained by computational methods, it appears that the PM3 parameters most accurately reflect the energy differences between the bis(methoxycarbonyl)methylide LUMO and the cyclooctyne HOMO; in the cases of **1a-f** and **1k**, they are larger than 9 eV, while they are smaller than 9 eV in the cases of **1g-j** and **1l**.

Pyridinium dicyanomethylides **4** underwent a facile cycloaddition with **2** to afford the corresponding indolizines in nearly quantitative yield [15]. In contrast, pyridinium bis(methoxycarbonyl)methylides **1** often react sluggishly with **2** as exemplified in the cases of **1d** and **1k** (see, Table 1). For comparison, the values of the energy difference between dicyanomethylide LUMO and cyclooctyne HOMO are shown in Table 5. The energy differences of LUMO(**1**)-HOMO(**2**) and LUMO(**4**)-HOMO(**2**) are also summarized in Table 6. As mentioned above, these results are in qualitative agreement with those found experimentally, with the exception of those from the INDO method, where the values of the energy differences between dicyanomethylide **4**(LUMO)-cyclooctyne **2**(HOMO) are smaller than those of bis(methoxycarbonyl)methylide **1**(HOMO)-cyclooctyne **2**(LUMO). Thus, showing that, in these cases the PM3 method is better at predicting qualitatively the relative reactivity of this type of the reaction.

EXPERIMENTAL

General.

Melting points were taken on a Yanagimoto micro melting point apparatus and were uncorrected. The ^1H nmr spectra were measured either on a JEOL JNM-EX270 (270 MHz), or JNM-ALPHA500 (500 MHz) instrument. The ^{13}C nmr spectra were recorded either on a JNM-EX270 or JNM-ALPHA500 pulsed Fourier-transform spectrometer operating at 67.80 MHz and 125.65 MHz, respectively. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Either partial proton decoupling or the DEPT method was used to distinguish between individual carbon atoms. Preparative medium-pressure liquid chromatography was carried out using a column (25 x 310 mm) prepacked with silica gel (Lobar, LiChroprep Si60, Merck). Pyridinium bis(methoxycarbonyl)methylides **1** were prepared according to the method of Kobayashi *et al.* [18]. Compounds **1b-n** have been described by us in previous reports [14] without microanalytical and spectroscopic data. Therefore, in this occasion, selected physical and spectroscopic data are given as follows.

Pyridinium bis(methoxycarbonyl)methylides **1**.

4-Methylpyridinium bis(methoxycarbonyl)methylide (**1b**).

This compound was obtained in 49% yield, mp 194-196°; uv (chloroform): λ_{max} (log ϵ) 410 (3.399), 253 (4.117), 300 (2.570) nm; ir (potassium bromide disk): 1700 cm^{-1} ; ^1H nmr: δ 2.63 (s, 3H, CH_3), 3.71 (s, 6H, OCH_3), 7.54 (d, $J = 6.5$ Hz, 2H, H-3, 5), 8.39 (d, $J = 6.5$ Hz, 2H, H-2, 6); ^{13}C nmr: δ 21.8 (CH_3), 50.4 (OCH_3), 96.3 (ylidic C), 126.5 (C-3, 5), 149.2 (C-2, 6), 155.4 (C-4), 165.3 (C=O).

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{NO}_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 58.91; H, 5.86; N, 6.26.

4-Ethylpyridinium bis(methoxycarbonyl)methylide (**1c**).

This compound was obtained in 15% yield, mp 196-197°; uv (chloroform): λ_{max} (log ϵ) 413 (3.796), 243 (4.348) nm; ir (potassium bromide disk): 1710 cm^{-1} ; ^1H nmr: δ 1.36 (t, $J = 7.6$ Hz, 3H, CH_3), 2.90 (q, $J = 7.6$ Hz, 2H, CH_2), 3.72 (s, 6H, OCH_3), 7.52 (d, $J = 6.8$ Hz, H-3, 5), 8.41 (d, $J = 6.8$ Hz, 2H, H-2, 6); ^{13}C nmr: δ 94.9 (ylidic C), 12.9 (CH_3), 27.6 (CH_2), 48.7 (OCH_3), 125.4 (C-3, 5), 149.6 (C-2, 6), 160.9 (C-4), 163.5 (C=O).

Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{NO}_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.55; H, 6.22; N, 5.73.

4-Propylpyridinium bis(methoxycarbonyl)methylide (**1d**).

This compound was obtained in 53% yield, mp 208-210°; uv (chloroform): λ_{max} (log ϵ) 409 (3.408), 249 (4.264) nm; ir (potassium bromide disk): 1730 cm^{-1} ; ^1H nmr: δ 1.03 (t, $J = 7.3$ Hz, 3H, CH_3), 1.73-1.80 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 2.81 (t, $J = 7.9$ Hz, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 3.72 (s, 6H, OCH_3), 7.49 (d, $J = 6.7$ Hz, H-3, 5), 8.41 (d, $J = 6.7$ Hz, H-2, 6); ^{13}C nmr: δ 13.0 (CH_3), 21.9, 36.3 (each CH_2), 48.7 (OCH_3), 94.9 (ylidic C), 125.8 (C-3, 5), 149.5 (C-2, 6), 159.4 (C-4), 163.5 (C=O).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.88; H, 6.86; N, 5.51.

4-*i*-Propylpyridinium bis(methoxycarbonyl)methylide (**1e**).

This compound was obtained in 28% yield, mp 188-191°; uv (chloroform): λ_{max} (log ϵ) 411 (3.255), 249 (4.119), 282 (3.342) nm; ir (potassium bromide disk): 1730 cm^{-1} ; ^1H nmr: δ 1.32-1.39 (m, 6H, CH_3), 3.12 (hep., $J = 7.0$, 1H, CH), 3.72 (s, 6H, OCH_3), 7.54 (d, $J = 6.8$ Hz, 2H, H-3, 5), 8.43 (d, $J = 6.8$ Hz, 2H, H-2, 6); ^{13}C nmr: δ 21.9 (CH_3), 33.0 (CH), 48.8 (OCH_3), 94.9 (ylidic C), 124.1 (C-3, 5), 149.8 (C-2, 6), 164.8 (C-4), 163.6 (C=O).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.95; H, 6.87; N, 5.42.

4-*t*-Butylpyridinium bis(methoxycarbonyl)methylide (**1f**).

This compound was obtained in 37% yield, mp 198-199°; uv (chloroform): λ_{max} (log ϵ) 410 (3.369), 250 (4.127), 282 (3.153) nm; ir (potassium bromide disk): 1710 cm^{-1} ; ^1H nmr: δ 1.41 (s, 9H, CH_3), 3.72 (s, 6H, OCH_3), 7.66 (d, $J = 5.0$ Hz, 2H, H-3, 5), 8.44 (d, $J = 5.0$ Hz, 2H, H-2, 6); ^{13}C nmr: δ 29.4 (CH_3), 37.6 (q-C), 48.8 (OCH_3), 94.7 (ylidic C), 123.1 (C-3, 5), 149.6 (C-2, 6), 163.5 (C=O), 167.0 (C-4).

Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.27; H, 7.31; N, 5.31.

4-Phenylpyridinium bis(methoxycarbonyl)methylide (**1g**).

This compound was obtained in 55% yield, mp 245-247°; uv (chloroform): λ_{max} (log ϵ) 447 (3.649), 313 (4.375), 281 (4.045) nm; ir (potassium bromide disk): 1750 cm^{-1} ; ^1H nmr: δ 3.74 (s, 6H, OCH_3), 7.55-7.63 (m, 3H, H-3, 5 + Ph-H), 7.68-7.75 (m, 2H, Ph-H), 7.84 (d, $J = 7.3$ Hz, 2H, Ph-H), 8.56 (d, $J = 6.7$ Hz, 2H, H-2, 6); ^{13}C nmr: δ 48.9 (OCH_3), 95.0 (ylidic C), 122.8 (C-3, 5), 127.4 (*p*-CH), 129.2 (*m*-CH), 131.1 (*o*-CH), 133.8 (*ipso*-C), 150.1 (C-2, 6), 152.1 (C-4), 163.5 (C=O).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{NO}_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.06; H, 5.25; N, 4.83.

4-Acetylpyridinium bis(methoxycarbonyl)methylide (**1h**)

Compound **1h** (4-CH₃CO) was obtained in 39% yield, mp 147-149°; uv (chloroform): λ_{\max} (log ϵ) 508 (3.560), 248 (4.111), 279 (3.255) nm; ir (potassium bromide disk): 1700 cm⁻¹; ¹H nmr: δ 2.72 (s, 3H, CH₃), 3.75 (s, 6H, OCH₃), 8.05 (d, J = 7 Hz, 2H, H-3, 5), 8.81 (d, J = 7 Hz, 2H, H-2, 6); ¹³C nmr: δ 26.3 (CH₃), 50.8 (OCH₃), 97.9 (ylidic C), 123.6 (C-3, 5), 144.1 (C-2, 6), 150.1 (C-4), 164.8 (C=O), 193.7 (C=O).

Anal. Calcd. for C₁₂H₁₃NO₅: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.32; H, 5.18; N, 5.45.

4-Benzoylpyridinium bis(methoxycarbonyl)methylide (**1i**)

This compound was obtained in 32% yield, mp 232-234°; uv (chloroform): λ_{\max} (log ϵ) 497 (3.670), 247 (4.735), 270 (4.320) nm; ir (potassium bromide disk): 1710, 1650 cm⁻¹; ¹H nmr: δ 3.77 (s, 6H, OCH₃), 7.57 (t, J = 7.6 Hz, 2H, Ph-*m*-H), 7.72 (t, J = 7.6 Hz, 1H, Ph-*p*-H), 7.84 (d, J = 7.8 Hz, 2H, Ph-*o*-H), 7.92 (d, J = 7.0 Hz, 2H, H-3, 5), 8.80 (d, J = 7.0 Hz, 2H, H-2, 6); ¹³C nmr: δ 50.8 (OCH₃), 98.0 (ylidic C), 125.0 (C-3, 5), 125.8, 129.1, 130.2 (each Phenyl-C), 146.8 (C-4), 149.4 (C-2, 6), 165.1 (C=O), 196.4 (C=O).

Anal. Calcd. for C₁₇H₁₅NO₅: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.94; H, 4.84; N, 4.49.

4-Cyanopyridinium bis(methoxycarbonyl)methylide (**1j**)

This compound was obtained in 10% yield, mp 192-193°; uv (chloroform): λ_{\max} (log ϵ) 513 (3.614), 248 (4.037), 272 (3.319) nm; ir (potassium bromide disk): 2220, 1700, 1660 cm⁻¹; ¹H nmr: δ 3.77 (s, 6H, OCH₃), 7.80 (d, J = 6.4 Hz, 2H, H-3, 5), 8.89 (d, J = 6.4 Hz, 2H, H-2, 6); ¹³C nmr: δ 49.2 (OCH₃), 97.3 (ylidic C), 114.7 (CN), 121.8 (C-4), 128.2 (C-3, 5), 149.5 (C-2, 6), 163.0 (C=O).

Anal. Calcd. for C₁₁H₁₀N₂O₄: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.63; H, 4.23; N, 11.99.

3,5-Dimethylpyridinium bis(methoxycarbonyl)methylide (**1k**)

This compound was obtained in 36% yield, mp 288-290°; uv (chloroform): λ_{\max} (log ϵ) 417 (3.308), 251 (4.220), 271 (3.733) nm; ir (potassium bromide disk): 1710 cm⁻¹; ¹H nmr: δ 2.47 (s, 6H, CH₃), 3.71 (s, 6H, OCH₃), 7.78 (br.s, 1H, H-4), 8.20 (br.s, 2H, H-2, 6); ¹³C nmr: δ 18.3 (CH₃), 50.5 (OCH₃), 97.0 (ylidic C), 136.2 (C-3, 5), 143.4 (C-4), 147.2 (C-2, 6), 165.4 (C=O).

Anal. Calcd. for C₁₂H₁₅NO₄: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.60; H, 6.34; N, 5.83.

Isoquinolinium bis(methoxycarbonyl)methylide (**1l**)

This compound was obtained in 43% yield, mp 233-234°; uv (chloroform): λ_{\max} (log ϵ) 417 (3.559), 252 (4.227), 340 (3.412), 312 (3.535) nm; ir (potassium bromide disk): 1700, 1640 cm⁻¹; ¹H nmr: δ 3.75 (s, 6H, OCH₃), 7.83-7.88 (m, 1H, H-7), 7.98 (d, J = 7 Hz, 1H, H-5), 8.02-8.04 (m, 2H, H-6, 8), 8.17 (d, J = 7 Hz, 1H, H-4), 8.32 (d, J = 7 Hz, 1H, H-3), 9.30 (s, 1H, H-1); ¹³C nmr: δ 50.7 (OCH₃), 97.1 (ylidic C), 123.5 (C-4), 126.7 (C-5), 127.6 (C-8a), 129.7 (C-7), 130.0 (C-8), 135.5 (C-6), 136.2 (C-4a), 141.2 (C-3), 153.5 (C-1), 165.6 (C=O).

Anal. Calcd. for C₁₄H₁₃NO₄: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.58; H, 5.02; N, 5.14.

3-Methylpyridinium bis(methoxycarbonyl)methylide (**1m**)

This compound was obtained in 56% yield, mp 240-241°; uv (chloroform): λ_{\max} (log ϵ) 420 (3.363), 252 (4.194), 300 (2.534), 270 (3.671) nm; ir (potassium bromide disk): 1700, 1660, 1635, 1620 cm⁻¹; ¹H nmr: δ 2.52 (s, 3H, CH₃), 3.72 (s, 6H, OCH₃), 7.63 (dd, J = 6.8, 8.0 Hz, 1H, H-5), 7.98 (br.d, J = 8.0 Hz, 2H, H-4, 6), 8.40 (br.s, 1H, H-2); ¹³C nmr: δ 18.5 (CH₃), 50.5 (OCH₃), 97.2 (ylidic C), 125.4 (C-5), 136.9 (C-3), 142.4 (C-4), 147.4 (C-6), 149.8 (C-2), 165.3 (C=O).

Anal. Calcd. for C₁₁H₁₃NO₄: C, 59.19; H, 5.87; N, 6.28. Found: C, 59.30; H, 5.84; N, 6.27.

3-Ethylpyridinium bis(methoxycarbonyl)methylide (**1n**)

This compound was obtained in 47% yield, mp 199-200°; uv (chloroform): λ_{\max} (log ϵ) 419 (3.380), 251 (4.214), 300 (2.694), 270 (3.615) nm; ir (potassium bromide disk): 1710, 1640 cm⁻¹; ¹H nmr: 1.34 (t, J = 7 Hz, 3H, CH₃), 2.82 (q, J = 7 Hz, 2H, CH₂), 3.72 (s, 6H, OCH₃), 7.63 (dd, J = 7, 8 Hz, 1H, H-5), 7.97 (d, J = 8 Hz, 1H, H-4), 8.40 (br.s, 2H, H-2, 6); ¹³C nmr: δ 10.1 (CH₃), 24.6 (CH₂), 48.8 (OCH₃), 95.7 (ylidic C), 125.8 (C-5), 142.1 (C-3), 142.3 (C-4), 147.8 (C-6), 149.2 (C-2), 163.5 (C=O).

Anal. Calcd. for C₁₂H₁₅NO₄: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.80; H, 6.47; N, 5.86.

3-Benzoylpyridinium bis(methoxycarbonyl)methylide (**1o**)

This compound was obtained in 84% yield, mp 214-216°; uv (chloroform): λ_{\max} (log ϵ) 455 (3.412), 254 (4.086), 270 (2.992) nm; ir (potassium bromide disk): 1700, 1670 cm⁻¹; ¹H nmr: δ 3.75 (s, 6H, OCH₃), 7.59 (t, J = 8 Hz, 2H, Ph-*m*-H), 7.71 (t, J = 8 Hz, 1H, Ph-*p*-H), 7.84-7.89 (m, 3H, H-5, Ph-*o*-H), 8.55 (d, J = 8 Hz, H-4), 8.80 (d, J = 6 Hz, H-6), 8.95 (s, 1H, H-2); ¹³C nmr: δ 49.0 (OCH₃), 96.3 (ylidic C), 126.3 (C-5), 128.6, 129.6, 133.7 (each Phenyl-C), 134.9 (C-3), 141.9 (C-4), 149.9 (C-6), 152.0 (C-2), 163.4 (C=O), 190.2 (C=O).

Anal. Calcd. for C₁₇H₁₅NO₅: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.10; H, 4.83; N, 4.20.

3-Chloropyridinium bis(methoxycarbonyl)methylide (**1p**)

This compound was obtained in 0.3% yield, mp 235-237°; uv (chloroform): λ_{\max} (log ϵ) 447 (3.449), 249 (4.205), 270 (3.585) nm; ir (potassium bromide disk): 1660, 1640 cm⁻¹; ¹H nmr: δ 3.74 (s, 6H, OCH₃), 7.66 (dd, J = 6, 7 Hz, 1H, H-5), 8.07 (d, J = 7 Hz, 1H, H-4), 8.56 (d, J = 6 Hz, 1H, H-6), 8.68 (s, 1H, H-2); ¹³C nmr: δ 51.0 (OCH₃), 96.8 (ylidic C), 126.1 (C-5), 133.7 (C-3), 141.1 (C-4), 148.0 (C-6), 148.7 (C-2), 165.0 (C=O).

Anal. Calcd. for C₁₀H₁₀ClNO₄: C, 49.30; H, 4.14; N, 5.75. Found: C, 49.25; H, 4.15; N, 5.49.

3-Bromopyridinium bis(methoxycarbonyl)methylide (**1q**)

This compound was obtained in 16% yield, mp 212-215°; uv (chloroform): λ_{\max} (log ϵ) 448 (3.483), 249 (4.234), 277 (3.623) nm; ir (potassium bromide disk): 1700, 1640 cm⁻¹; ¹H nmr: δ 3.74 (s, 6H, OCH₃), 7.59 (dd, J = 6, 8 Hz, 1H, H-5), 8.21 (d, J = 8 Hz, 1H, H-4), 8.59 (d, J = 6 Hz, H-6); ¹³C nmr: δ 49.0 (OCH₃), 96.2 (ylidic C), 119.4 (C-3), 127.0 (C-5), 144.9 (C-4), 149.5 (C-6), 150.5 (C-2), 163.3 (C=O).

Anal. Calcd. for C₁₀H₁₀BrNO₄: C, 41.69; H, 3.50; N, 4.86. Found: C, 41.75; H, 3.50; N, 4.86.

General Procedure for the Reactions of bis(methoxycarbonyl)-methylides **1a-n** with Cyclooctyne.

A mixture of **1** (0.32-2.14 mmol) and cyclooctyne **2** (0.64-3.00 mmol) was heated in refluxing toluene (10 ml) for 1-24 hours. The mole ratios of **1** to **2** were 1.2-2.0. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel (30 g) with hexane-ethyl acetate (9:1 to 8:2) and ethyl acetate to give the corresponding indolizines **2**. The results are summarized in Tables 1-3.

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- [*] Author to whom corresponding should be addressed (E-mail: Kiyoshi.Matsumoto@ma1.seikyoku.ne.jp or kimatsu@ip.media.kyoto-u.ac.jp).
- [†] Present address: Department of Materials Science and Chemical Engineering, Faculty of Engineering, Shizuoka University, Johoku 3-5-1, Hamamatsu, Shizuoka 432-8561, Japan.
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