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The resonance energies and magnetic properties of cyclazines such as pyrido[2,1,6-cd]quinolizine (1) and pyrido[2,1,5-de]quinolizine (6) were calculated by means of Aihara's TRE. Consequently, cycl[3.2.2]azines and cycl[3.3.3]azines were predicted to be aromatic, while cycl[4.3.2]azines were predicted to be anti-aromatic.

The chemistry of cyclazines has attracted attention for their synthetic and physicochemical as well as biological viewpoints [1,2]. A number of cyclazine derivatives have been synthesized and many investigators reported molecular orbital treatment of cyclazines [2]. On the basis of ^{1}H nmr spectra of these compounds, cycl[3.2.2]azines 1 are predicted to be diatropic, on the other hand, cycl[3.3.3]-azines 6 paratropic [2]. Aihara's graph theory of aromaticity (TRE) has been one of the most important principles in the study of the aromaticity and stability of molecules [3]. This theory is also a useful tool for evaluating the magnetic properties of molecules. In a previous paper [4], we reported that the stability and resonance energy as well as the magnetic properties of heterocycle-annulated 1-aza-azulenes can be elucidated by means of Aihara's TRE and Gimarc's topological charge stabilization rule (TCS rule) [5]. In this paper we describe the origin of the aromaticity and magnetic property of cyclazines in terms of TRE and TCS rules. TRE calculations were carried out with the

Pyrido[2,1,6-cd]pyrrolizines 1-4 and TRE.

Compound 1 is related to annulenes as well as to nonalternant hydrocarbons; that is, it can be considered as an amino-substituted [10]annulene and at the same time as an isoelectronic with aceindenylanion 5. The largest charge density of anion 5 is at the central carbon atom [8].
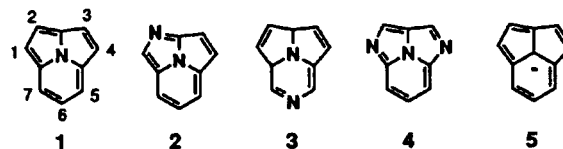
According to Gimarc's TCS rule [5], compound 1 can be designed by replacing the central carbon atom by a nitrogen. The calculated resonance energies and circuit resonance energies for 1-4 and aceindenyl anion 5 are given in Table 1. The resonance energy per π electron (REPE)

Table 1

Resonance Energies and Circuit Resonance Energies of Compounds 1-5

| | RE | REPE | | | Circuit resonance energies | | | | |
			r_1	r_2	r_3	r_4	r_5	r_6	r_7
1	0.4002	0.0333	0.0715	0.0715	0.0294	-0.0127	0.0358	0.0358	0.0651
2	0.3725	0.0310	0.0620	0.0720	0.0245	-0.0063	0.0326	0.0341	0.0570
3	0.3635	0.0303	0.0701	0.0701	0.0156	-0.0110	0.0334	0.0334	0.0585
4	0.3618	0.0302	0.0519	0.0519	0.0740	-0.0028	0.0263	0.0263	0.0419
5	0.4012	0.0334	0.0772	0.0772	0.0642	-0.0298	0.0523	0.0523	0.0123

RE: Resonance energy (in β units). REPE: Resonance energy per π electron (in β units). Circuit resonance energy (in β units).

HMO method [6]. Hess and Schaad evaluated the heteroatom parameters for the amine nitrogen and the imine nitrogen [7]. In this paper, we adopted these values.

values of compounds 1-4 were calculated to be 0.0302β-0.0333β and were similar to those of pyrrole (0.0404β), pyridine (0.0353β), and indolizine (0.0404β) [3]. In order

to clarify the origin of the stability and aromaticity, we calculated the circuit resonance energies of compounds 1-5 by TRE. The π-electron ring system in compounds 1-5 consisted of seven-ring components, from r_1 to r_7, as shown in Figure 1. As shown in Table 1, the 8π-electron ring (r_4) was predicted to be antiaromatic with a negative
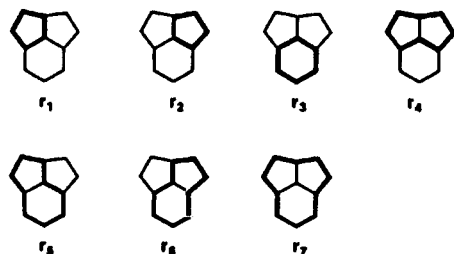
Figure 1. Geometrically unidentical π-electron circuits.

resonance energy; however, the relative value of the circuit resonance energy (r_4) for compounds 1-4 decreased with the number of nitrogen atoms. The circuit resonance energies of the indolizine part (r_5 or r_6) of 1-4 were small positive values. The values of the circuit resonance energy of the 10π-peripheral part (r_7) increased with the number of nitrogen atoms, while the value of the 6π-electron ring (r_3) decreased. Thus, 1-3 were stabilized as the 6π-pyrrole-10π-peripheral system. On the other hand, 4 was stabilized as the 6π-pyrrole-6π-pyridine system. The ^{1}H nmr spectra of compounds 1-4 are listed in Table 2 [2].

Compounds 1-4 are diatropic and resonated at the aromatic proton region. A comparison of the ^{1}H nmr spectra of 1 and 2 reveals a deshielding of 1.26 ppm, which is brought about by the anisotropic contribution of the peripheral nitrogen to the proton of the adjacent carbon atom. The peri interaction to the proton in position 3 gives rise to a deshielding of 0.15 ppm. The calculated circuit currents and bond-currents of 1-5 are given in Table 3. The plus and minus signs in Table 3 indicate diatropism and paratropism, respectively. Large diatropism was predicted to arise from r_7, while paratropism was predicted to arise from r_4. The diatropic effect decreased with the number of nitrogen atoms. The chemical shift of the six-membered ring protons of compound 1 is expected to appear in the largest downfield, while that of 3 is expected to resonate in the highest upfield by comparison with their bond-current values. But this prediction did not agree with observed chemical shifts. This result can be explained by the superposition of two contributions, a ring current and an anisotropic effect.

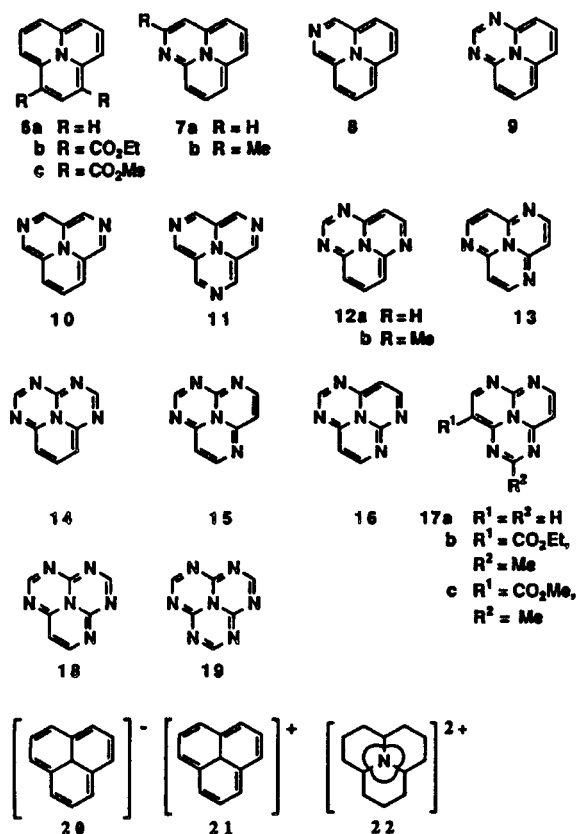### Pyrido[2,1,5-de]quinolizines 6-19 and TRE.

Pyrido[2,1,5-de]quinolizine (6a) has 14π electrons. The calculated resonance energies, REPE, and circuit resonance energies for cycl[3.3.3]azines are given in Table 4. Phenalene is remarkable in that it gives rise to a relatively stable anion 20 and cation 21. These mononegative and monopositive ions have the same resonance energies, which are seemingly large enough to justify their stability

Table 2

^{1}H NMR Spectra of Cyclazines [2]

	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9
1	7.20	7.51	7.51	7.20	7.86	7.59	7.86		
2	8.45	-	7.65	7.30	7.96	7.51	7.82		
3	7.44	7.64	7.64	7.44	9.21	-	9.21		
4	-	8.70	8.70	-	8.12	8.12	8.12		
6a	2.07	3.65	2.07	2.07	6.35	2.07	2.07	3.65	2.07
6b	-	7.16	-	6.77	6.14	5.23	5.23	6.14	6.77
7b	-	-	3.71	3.84	5.40	4.24	5.64	4.24	4.28
12b	-	-	-	4.97	7.07	-	5.81	6.77	5.35
17b	-	-	-	6.28	8.15	-	7.23	7.97	6.81

Table 3

Circuit Currents and Bond-Currents of Compounds 1-5

	Circuit currents (in benzene, I_o units)							Bond-currents (in benzene, I_o units)		
	r_1	r_2	r_3	r_4	r_5	r_6	r_7	r_1	r_2	r_3
1	0.1238	0.1238	0.1321	-0.0439	0.2231	0.2231	0.5181	0.8211	0.8211	1.0963
2	0.1073	0.1248	0.1102	-0.0218	0.2029	0.2132	0.4540	0.7425	0.7702	0.9803
3	0.1215	0.1215	0.0700	-0.0379	0.2081	0.2081	0.4660	0.7576	0.7576	0.9522
4	0.0900	0.0900	0.3328	-0.0095	0.1638	0.1638	0.3333	0.5775	0.5775	0.9937
5	0.1338	0.1338	0.2888	-0.1032	0.3261	0.3261	0.0979	0.4545	0.4545	1.0388

6a R = H
b R = CO₂Et
c R = CO₂Me

7a R = H
b R = Me

8

9

10

11

12a R = H
b R = Me

13

14

15

16

17a R¹ = R² = H
b R¹ = CO₂Et, R² = Me
c R¹ = CO₂Me, R² = Me

18

19

20

21

22

[3]. Anion **20** has a nonbonding molecular orbital. The HMO charge densities of **20** were calculated to be 0.166 at positions 1, 3, 4, 6, 7, and 9, and to be 0.000 at the other positions [2]. According to the TCS rule, nitrogen atoms are thus situated at the high-charge density site in

20 to stabilize the molecules. Nitrogen atoms, as well as introduction of electron withdrawing groups in the active positions 1, 3, 4, 6, 7, and 9, lowers the energy of the HOMO, while nitrogen atoms in non-active positions 2, 5, 8, and central carbon do not change the energy of the
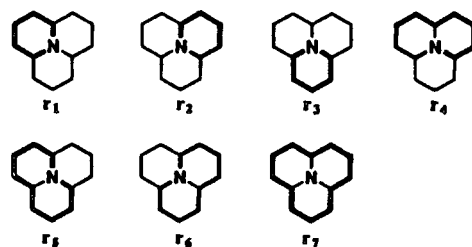

Figure 2. Geometrically unidentical π-electron circuits.

HOMO [2]. The resonance energy value of **6a** is smaller than that of the isoelectronic compound **20**. This result is attributable to anti-aromaticity in the 12π-peripheral system (r₇). Substituting cyclazines **8, 10,** and **11** with nitrogen atoms at the non-active positions produce more unstable compounds than **6a** when comparing their resonance energies. For example, compound **11** was predicted to be anti-aromatic with negative resonance energy. The origin of this instability is due to the larger 12π-peripheral system. Dication **22** was predicted to be aromatic with a positive resonance energy. The value of the circuit resonance energy (r₇) of **22** changed from a negative to a positive value. A stabilizing effect by introduction of nitrogen atoms is to be expected, having a dramatic influence on the nmr spectra. The ¹H nmr data of cyclazines are listed in Table 5 [2].

Table 4

Resonance Energies and Circuit Resonance Energies of Compounds 6-22

	RE	REPE	Circuit resonance energies						
			r₁	r₂	r₃	r₄	r₈	r₆	r₇
6a	0.1455	0.0104	0.0665	0.0665	0.0665	0.0221	0.0221	0.0221	-0.1020
7a	0.1964	0.0140	0.0324	0.0762	0.0819	0.0100	0.0100	0.0401	-0.0624
7b	0.1984	0.0124	0.0325	0.0735	0.0803	0.0101	0.0101	0.0389	-0.0570
8	0.0887	0.0063	0.0547	0.0690	0.0690	0.0203	0.0203	0.0228	-0.1319
9	0.2233	0.0160	0.0159	0.0849	0.0849	0.0048	0.0048	0.0481	-0.0432
10	0.0279	0.0020	0.0569	0.0569	0.0715	0.0186	0.0209	0.0209	-0.1734
11	-0.0360	-0.0026	0.0591	0.0591	0.0591	0.0191	0.0191	0.0191	-0.2379
12a	0.2236	0.0160	0.0270	0.0548	0.0881	0.0019	0.0168	0.0334	-0.0320
13	0.2111	0.0151	0.0564	0.0564	0.0564	0.0167	0.0167	0.0167	-0.0321
14	0.2221	0.0159	0.0364	0.0364	0.0947	0.0004	0.0240	0.0240	-0.0244
15	0.2119	0.0151	0.0374	0.0652	0.0593	0.0114	0.0114	0.0239	-0.0244
16	0.2136	0.0153	0.0334	0.0649	0.0649	0.0113	0.0113	0.0237	-0.0243
17a	0.2136	0.0153	0.0562	0.0597	0.0420	0.0211	0.0101	0.0144	-0.0215
18	0.2061	0.0147	0.0410	0.0456	0.0673	0.0079	0.0174	0.0174	-0.0190
19	0.1960	0.0140	0.0483	0.0483	0.0483	0.0129	0.0129	0.0129	-0.0150
20	0.4098	0.0293	0.0819	0.0819	0.0819	0.0254	0.0254	0.0254	-0.0116
22	0.4254	0.0355	0.0665	0.0665	0.0665	0.0221	0.0221	0.0221	0.0352

RE: Resonance energy (in β units). REPE: Resonance energy per π electron (in β units). Circuit resonance energy (in β units).

Table 5

Circuit Currents and Bond-Currents of Compounds 6-22

	Circuit currents (in benzene, I_o units)							Bond currents (in benzene, I_o units)		
	r_1	r_2	r_3	r_4	r_5	r_6	r_7	r_1	r_2	r_3
6a	0.2992	0.2992	0.2992	0.1985	0.1985	0.1985	-1.3764	-0.6802	-0.6802	-0.6802
7a	0.1457	0.3431	0.3685	0.0903	0.0903	0.3670	-0.8418	-0.5156	-0.0415	-0.0161
7b	0.1464	0.3308	0.3615	0.0905	0.0905	0.3500	-0.7694	-0.4420	0.0018	0.0325
8	0.2462	0.3104	0.3104	0.1823	0.1823	0.2049	-1.7800	-1.1692	-1.0825	-1.0825
9	0.0716	0.3819	0.3819	0.0432	0.0432	0.4327	-0.5836	-0.4255	0.2743	0.2743
10	0.2559	0.2559	0.3219	0.1673	0.1878	0.1878	-2.3410	-1.7300	-1.7300	-1.6435
11	0.2660	0.2660	0.2660	0.1720	0.1720	0.1720	-3.2119	-2.6018	-2.6018	-2.6018
12a	0.1214	0.2466	0.3966	0.0166	0.1511	0.3001	-0.4316	-0.1426	0.1317	0.4162
13	0.2536	0.2536	0.2536	0.1506	0.1506	0.1506	-0.4339	0.1209	0.1209	0.1209
14	0.1636	0.1636	0.4259	0.0038	0.2160	0.2160	-0.3291	0.0541	0.0541	0.5286
15	0.1683	0.2936	0.2668	0.1024	0.1024	0.2147	-0.3287	0.0444	0.2820	0.2552
16	0.1505	0.2922	0.2922	0.1017	0.1017	0.2136	-0.3278	0.0260	0.2796	0.2796
17a	0.2531	0.2687	0.1889	0.1895	0.0909	0.1298	-0.2904	0.2431	0.2976	0.1192
18	0.1846	0.2052	0.3027	0.0706	0.1565	0.1565	-0.2558	0.1560	0.1767	0.3600
19	0.2173	0.2173	0.2173	0.1157	0.1157	0.1157	-0.2022	0.2465	0.2465	0.2465
20	0.3685	0.3685	0.3685	0.2290	0.2290	0.2290	-0.1569	0.6695	0.6695	0.6695
22	0.2992	0.2992	0.2992	0.1985	0.1985	0.1985	0.4754	1.1716	1.1716	1.1716

The chemical shifts of the 6a ring protons (δ = 2.07-3.65) are among the highest fields reported for protons joined to trigonal carbon atoms. This high degree of shielding is evidence of a paramagnetic ring current in the 12π-peripheral which is in agreement with the values of the circuit currents. On the other hand, the dication 22 ring protons (δ = 9.67-10.41) appear downfield. The calculated circuit currents and bond-currents of 6-22 are shown in Table 5. As shown in Table 5, large diatropism of compound 22 was predicted to arise from the peripheral structure (i.e., structure r_7: $0.4754I_o$) in agreement with its chemical shift. The values of the circuit current of r_1-r_6 indicate diatropism, while the 12π-peripheral system (r_7) indicates large paratropism. The introduction of more than two nitrogen atoms into active positions converts the paratropic cyclazine into a diatropic π-system. The diatropic effect decreased with the number of nitrogen atoms.

Cycl[4.3.2]azines and TRE.

Cycl[4.3.2]azine 23a, which has not yet been synthesized, is anti-aromatic with a negative resonance energy (-0.0283β). On the other hand, the mononegative 24 and

23a R = H   24   25
b R = CO₂Et
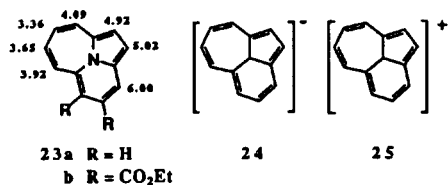
monopositive 25 ions of the corresponding hydrocarbon have the same resonance energies (0.01569β). The circuit

resonance energies and circuit currents of 23a are given in Figure 3. The calculated circuit resonance energies of
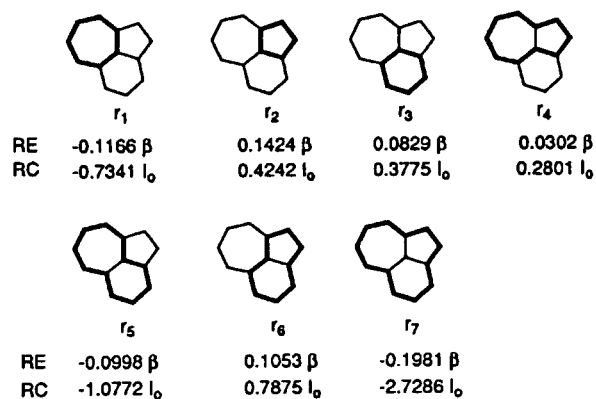

	r_1	r_2	r_3	r_4
RE	-0.1166 β	0.1424 β	0.0829 β	0.0302 β
RC	-0.7341 I_o	0.4242 I_o	0.3775 I_o	0.2801 I_o

	r_5	r_6	r_7
RE	-0.0998 β	0.1053 β	-0.1981 β
RC	-1.0772 I_o	0.7875 I_o	-2.7286 I_o

Figure 3. Circuit resonance energies and ring currents of 23a.
RE: Resonance energy (in β units).
RC: Ring current (in benzene, I_o units)

r_1, r_5, and r_7 showed negative values, while the values of r_2, r_3, r_4, and r_6 were positive. Consequently, cycl[4.3.2]azine 23a became unstable as the 6π-tropylium-12π-peripheral system. In the ^1H nmr spectrum of 23b, a paratropic effect of 1.7 ppm in the five- and six-membered rings, and one of at least 2.7 ppm in the seven-membered ring, follows comparison with suitable reference compounds. The different paratropism can be explained by the superposition of two ring systems, a diatropic indolizine and a paratropic [12]annulene moiety [9]. As shown in Figure 3, large paratropism was predicted from r_1, r_5, and r_7, while large diatropism was predicted from r_2 and r_6. As for compound 23a, the paratropism

effect due to the 6π-tropylium structure (*i.e.*, structure r_1: $-0.7341I_o$), the heterocycle part (*i.e.*, structure r_5: $-1.0772I_o$), and the peripheral 12π-structure (*i.e.*, structure r_7: $-2.7286I_o$) were the main contributors to the magnetic effect, although a small contribution came from the diatropism effect of the indolizine part (*i.e.*, structure r_6: $0.7875I_o$).

As mentioned above, cycl[3.2.2]azines and cycl[3.3.3]-azines were predicted to be aromatic, while cycl[4.3.2]-azines were predicted to be anti-aromatic and to conform to the TCS rule. Thus the TRE and TCS rules are very useful to clarify the origin of aromaticity and magnetic properties of complex systems such as heterocycle annulated compounds.

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